ORIGINAL ARTICLE

Surgical management of acromegaly: Long term functional outcome analysis and assessment of recurrent/residual disease

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ABSTRACT

Context: Functional growth hormone producing adenomas have long-term deleterious effects on the visual apparatus, the cardiovascular and musculoskeletal systems, and often predispose to malignancies. Since persistence of acromegaly affects outcome and quality of life, therapeutic interventions become mandatory.

Aim: This study represents an analysis of long-term clinical and endocrinal outcome of 115 patients of acromegaly after surgical management.

Setting and Design: Tertiary care retrospective study.

Materials and Methods: One hundred and fifteen patients (male:female ratio: 1:1.09) with acromegalic features were studied. Apart from acromegalic features, their main clinical presentation also included headache, diminution of vision, field defects, ptosis, irregular menstruation, diabetes insipidus, diabetes mellitus and hypertension. Six of them presented with apoplexy. Their preoperative endocrinal evaluation included basal and suppressed growth hormone (GH), prolactin and thyroid levels. On the basis of axial and coronal CT scan or multiplanar MR imaging or both, the tumors were classified according to their suprasellar and parasellar extension (Hardy's grade). Transnasal trans-sphenoidal surgery (TSS) ($n = 37$) and sublabial, rhinoseptal TSS ($n = 72$) were the preferred approaches. Six patients with significant parasellar extensions underwent trans-cranial explorations. The patients were followed up at 6 and 12 weeks and then at 6 monthly intervals. Hormonal and CT/MR evaluation were also done. Attainment of random GH value less than 2.5 µg/L, and the nadir GH value after oral glucose tolerance test (OGTT) less than 1 µg/L were used as the criteria of cure.

Findings: The patients were preoperatively in Hardy's tumor grade 0 (29), A (21), A+E (3), B (21), B+E (5), C (9), C+E (10), D (1) D+E (11), E (5), respectively. One hundred and one patients were available for follow-up (FU; median FU duration: 84 months; range: 6 to 132 months). Surgical cure was achieved in 73 patients following the first surgery; and, in 10 additional patients following a second intervention. No patient with a preoperative grade 0, A, B, C had a recurrence after attaining the initial remission. Recurrence after an initial cure occurred in 7 patients (overall remission rate following surgery: 75.24%).The preoperative grade of the latter patients was A+E:1, B+E:1, C+E:1, D:1, D+E:2, E:1, respectively. All these patients underwent subsequent radiotherapy (RT). The twelve patients with persistent symptoms and high GH levels following surgery underwent RT; six others with improved symptoms despite high GH levels were kept under strict observation. There was no surgical mortality.

Conclusions: A high remission rate without significant morbidity could be achieved following surgical intervention in acromegalic patients. Following surgery, tumors with greater than or equal to 3 cm suprasellar height and without parasellar extension had no clinical recurrence at FU. A continuous monitoring is mandatory to pick up relapsed cases as well as those who develop delayed signs of hypopituitarism. A subset of patients who show clinical improvement following surgery but still have higher GH levels may be followed up without additional therapy unless clinical signs reappear or the serum GH levels progressively increase.

Key words: Acromegaly, pituitary adenoma, surgery, trans-sphenoidal surgery

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Introduction

Acromegaly is caused in more than 99% of patients by the autonomous secretion of growth hormone (GH) from a benign monoclonal pituitary adenoma.[1] GH stimulates hepatic production of insulin-like growth factor-1 (IGF-1). Active acromegaly is associated with a 2-4 fold increase in the risk of mortality, mainly from cardiovascular complications, apoplectic events, malignancies and/or a rapidly expansile mass.[2-4] Approximately 22-30% of acromegalic patients harbor microadenomas; the rest of the patients, however, have macroadenomas, often with supra- and parasellar extensions.[5] Trans-sphenoidal surgery (TSS) is the treatment of choice and offers the best chance of rapid normalization of GH levels when compared with medical treatment and pituitary radiotherapy (RT).[6-10] Even in patients where remission is not possible because of invasiveness of tumor or its situation at a potentially dangerous site, surgery decreases the tumor burden and increases the effectiveness of adjunctive therapy. Studies have shown that many consequences related to soft tissue growth as well as the apparent risk of increased mortality in acromegalic patients may be reversed with appropriate therapy.[6,9]

Various biochemical criteria for the remission of GH levels following surgery for acromegaly have been suggested. They include a random GH value of less than 2.5 µg/L; the nadir GH value after oral glucose tolerance test (OGTT) of less than 1 µg/L; and, normal levels (after age-dependent normalization) of IGF-1.[6,11,12,13] The importance of adequate treatment leading to normalization of GH levels is highlighted by studies, which indicate that lowering GH levels to less than 2.5 µg/L reverses the premature mortality of acromegaly.[6,11,14]

We used the first two criteria of GH normalization (a random GH value of less than 2.5 µg/L; and, the nadir GH value after OGTT of less than 1 µg/L) to analyze the long-term follow-up (FU) clinical and endocrinal outcome of 115 acromegalic patients who underwent surgical management over a 13-year duration.

Materials and Methods

Between January 1992 and August 2005, 115 patients with GH-secreting pituitary adenoma and acromegaly were treated at our institute. Their data was prospectively recorded by senior residents in disease-specific proformas that included clinical evaluations, preoperative hormonal indices, neuroradiological and operative findings, postoperative hormonal indices, clinical outcome, complications and FU evaluations. The preoperative diagnosis of acromegaly was made on the basis of clinical examination of our patients and confirmed by biochemical evaluation of lack of suppression of GH to below 1.0 µg/L during OGTT.[11,15,16]

Patient population

There were 60 female and 55 male patients, ranging in age from 12 to 62 years (mean 34.0 ± 10.6 years). All patients had clinical features of acromegaly. The associated symptoms included headache, diminution of vision, field defects, ptosis, amenorrhea or oligomenorrhea, diabetes insipidus, diabetes mellitus and hypertension. Six patients presented with apoplexy.

Hormonal evaluation

The normal basal value for serum GH for our laboratory was at or below 10 µg/L. The preoperative basal GH levels were available for all 115 patients. The mean preoperative basal GH level in this study was 28.40 ± 20.42 µg/L. After OGTT suppression, the mean GH value reached 27.31 ± 20.86 µg/L. Serum-free thyroxine levels were evaluated in 27 patients. It was found to be below normal in 9 of these patients. Serum prolactin levels were higher than normal in 25 patients out of the 64 patients in whom it was carried out.

Criteria for biochemical cure

Random serum GH levels along with OGTT-suppressed levels were estimated after 6 weeks following surgical excision of the tumor. The remission criteria (as already mentioned) included the mean daily GH values of less than 2.5 µg/L; and, the nadir GH values of less than 1.0 µg/L after OGTT.[6,11,12] At FU, basal GH levels were assessed in 48 (41.7%); and, OGTT-suppressed GH levels at 0 and 60 minutes were performed in 88 (76.5%) out of the 115 patients. In our institute, IGF level was not routinely done in all patients, so normalization of age-specific IGF was not included as a criteria for cure.[15,16]

Classification of tumors according to their size

Tumors were classified (according to modified Hardy's classification) based on their degree of suprasellar and parasellar extension on preoperative contrast enhanced computerized tomographic (CT) scan, magnetic resonance (MR) imaging or both.[17,18] The tumor size was estimated by measuring the largest tumor diameter and its extensions on preoperative CT or MR images in the three planes.

Surgical approach

Sublabial rhinoseptal TSS was carried out in 72 patients and trans-nasal TSS in 37 patients. Six patients with significant parasellar extensions underwent a transcranial exploration via a frontotemporal, trans-sylvian approach. The sphenoid sinus was packed with a fat graft harvested from the abdominal wall or the thigh in all patients who underwent TSS. Fourteen patients (grade B+E:4, C:10) underwent reoperation via the TSS (*n*: 8) or the frontotemporal, trans-sylvian approach (*n* : 6) for residual tumor after being initially operated through the TSS. In 10 patients, the residual suprasellar component that could not be accessed during the initial surgery was removed during a subsequent surgery. Following the second surgery, the GH levels normalized in these patients.

Postoperative and follow-up status

The patients were followed up (with a clinical assessment, hormonal profile evaluation and CT/MR imaging) at 6 and 12 weeks after their discharge (usually on the 7th postoperative day) and then at 6 monthly intervals. The period of FU in this study ranged from 3 to 132 months (median 84 months); 14 of the 115 patients were lost to FU.

Results

In our series, the Hardy's grading of pituitary adenoma was 0 in 29 patients, A in 21, A+E in 3, B in 21, B+E in 5, C in 9, C+E in 10, D in 1, D+E in 11, and E in 5 patients, respectively [Table 1]. Only 7 patients in the series had a tumor size less than 10 mm in all three dimensions on CT/MR imaging.

The results of the 101 patients available for FU are summarized in Table 2. Surgical cure (with hormonal remission) was achieved in 73 patients following the first surgery. In 10 other patients, the residual suprasellar component that could not be accessed during the initial surgery was removed during a subsequent surgery after the FU CT scan performed after 6 weeks. Following the second surgery, the GH levels normalized in these patients.

After surgery, 14 out of 34 patients who had abnormalities of menstruation in the preoperative period resumed normal cycle on supplementation therapy. Diabetes insipidus improved in 4 out of 22 patients and 4 out of 21 hypothyroid patients became euthyroid. Eleven patients without preoperative evidence of diabetes insipidus developed postoperative diabetes insipidus. This diabetes insipidus was transient in 7 and had improved at FU evaluation; in 4 of them, however, diabetes insipidus was sustained requiring regular vasopressin supplementation. Hypertension improved in 4 out of 11 patients and diabetes mellitus improved in 4 out of 14 patients at FU [Table 3].

Of the 83 patients who initially showed improvement in their GH levels following surgery, recurrence after the initial

remission was seen in 7 patients. All these patients were referred for RT. The preoperative Hardy's grade of these patients was A+E in 1, B+E in 1, C+E in 1, D in 1, D+E in 2 and E in 1 patient, respectively. No patient whose initial preoperative grade was 0, A, B or C had a recurrence after the initial remission was achieved [Table 4].

The hormonal status of the 101 patients available for FU is summarized in Table 5. There was postoperative improvement in the mean postoperative basal and stimulated GH levels in all the Hardy's groups. The patients with cavernous sinus involvement (E) and those with significant suprasellar tumor (group D) had distinctly higher values of GH at FU compared to rest of the groups [Figure 1].

In 18 patients, the hormonal levels did not return to normal following surgery. 12 of these patients who had a persistence of their symptoms of acromegaly as well as elevated GH levels were referred for RT [Table 1]. Six other patients with significant improvement in postoperative clinical manifestations despite persistently high GH levels were kept under regular clinical and radiological observation as they were extremely reluctant to undergo further interventions following the first surgery [Table 6]. Their basal and stimulated GH levels following surgery remained much higher than that observed in the FU period in the responder group. These patients were planned to undergo reoperation or RT in case the clinical symptoms reappeared or the hormonal levels progressively increased.

Complications

Following surgery, 8 patients developed hypothyroidism and/or hypogonadism requiring life-long hormonal supplementation. Eleven patients developed perioperative diabetes insipidus

Table 1: Preoperative Hardy's grade of patients with acromegaly (*n*=115)

Grade	Definition	Number of patients
0	Intra-sellar	29
A	SSH <1 cm	21
A+E	SSH <1 cm+PS	3
B	SSH: 1-2 cm	21
B+E	SSH: 1-2 cm+PS	5
C	SSH: 2-3 cm	9
C+E	SSH: 2-3 cm+PS	10
D	SSH >3 cm	1
D+E	SSH >3 cm+PS	11
E	PS	5

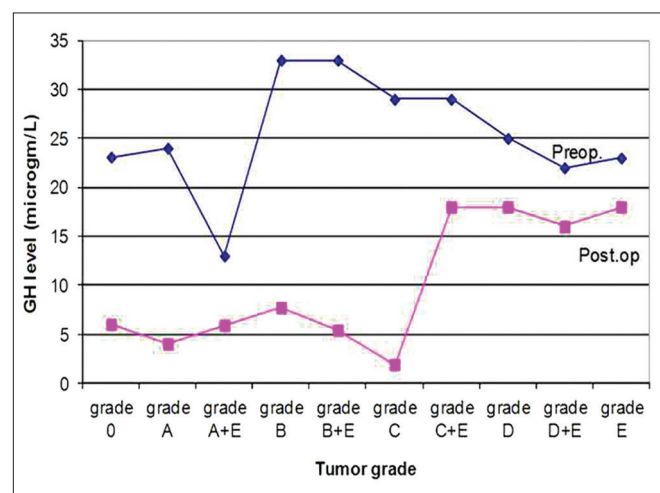SSH – Suprasellar height; PS – Parasellar extension

Figure 1: Graph showing that there was considerable improvement in the mean postoperative basal and stimulated GH levels in all the Hardy's groups when compared to preoperative levels. The patients with cavernous sinus involvement (E) and those with significant suprasellar tumor (group D) had distinctly higher values of GH at follow-up compared to rest of the groups

Table 2: Follow-up (median duration: 84 months; range: 6 to 132 months) results following surgery in acromegalic patients (*n* : 115)
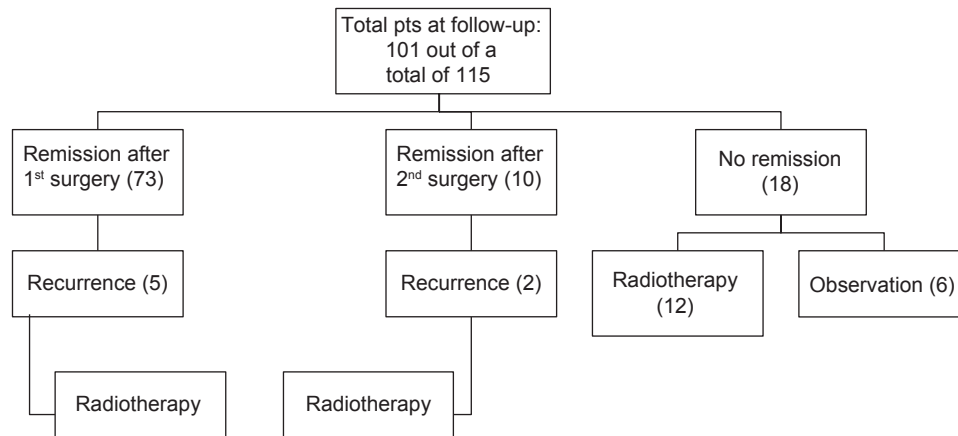
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                    ┌─────────────────────┐
                    │ Total pts at follow-up: │
                    │   101 out of a      │
                    │   total of 115      │
                    └─────────────────────┘
        ┌──────────────────┬──────────────────────┐
┌───────────────┐  ┌───────────────┐   ┌───────────────┐
│ Remission after│  │ Remission after│   │ No remission  │
│ 1st surgery (73)│ │ 2nd surgery (10)│  │    (18)       │
└───────────────┘  └───────────────┘   └───────────────┘
        │                  │             ┌──────┴──────┐
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│ Recurrence (5) │  │ Recurrence (2) │ │Radiotherapy│ │Observation │
└───────────────┘  └───────────────┘ │   (12)    │ │    (6)     │
        │                  │          └──────────┘ └────────────┘
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│ Radiotherapy  │  │ Radiotherapy  │
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Table 3: Status of clinical symptoms at follow up (101 out of 115 patients available at follow-up)

Symptoms	Same	Improved	Deteriorated
Headache	12	75	2
Diminution of vision	25	10	-
Field cut	8	3	4
Ptosis	2	1	-
Amenorrhea	13	10	
Oligomenorrhea	3	4	4
Diabetes insipidus	14	4	4
Diabetes mellitus	10	4	-
Hypothyroid	9	4	8
Hypertension	7	4	-

Table 4: Characteristics of patients showing recurrence (*n*=7) after initial remission (*n*=83) following surgery

Hardy's grade	Definition	Number of patients with recurrence after initial remission	Duration of FU (median months)
o, A, B, C	Max. SSH<3 cm, No PS	0	-
A+E	SSH<1 cm+PS	1	36
B+E	SSH: 1-2 cm+PS	1	34
C+E	SSH: 2-3 cm+PS	1	24
D	SSH>3 cm	1	18
D+E	SSH>3 cm+PS	2	36
E	PS	1	48

SSH: Suprasellar height; FU: Follow-up; PS: Parasellar extension

after surgery. In 4 of them, the diabetes insipidus continued in the available FU period requiring regular vasopressin supplementation. Seven patients developed cerebrospinal fluid rhinorrhea following TSS requiring closed lumbar drainage for 3 days along with acetazolamide (250 mg q.i.d.) administration. There was no perioperative mortality in the series.

Radiotherapy

Nineteen patients received RT 45-50Gy in fractioned doses. Among these, 7 patients had recurrence of tumor and other 12 patients had persistent high GH level and acromegalic symptoms after surgery. The optic apparatus was protected either by three-dimensional conformal RT or intensity-modulated RT technique.

Discussion

In acromegalic patients, successful surgical excision of the functioning pituitary adenoma normalizes serum GH and IGF-1 concentrations. This helps in providing clinical relief to these patients in several ways. The excess soft tissue mass and skin thickening decrease. Bony growth that has already taken place does not reduce but its further enlargement is prevented.[6,19] Headache, visual acuity compromise, visual field impairment and cranial nerve palsies improve. Hypertension (present in nearly 30% of patients due to volume overload and structural changes in the vascular system), and diabetes mellitus, that are often coexisting in these patients, may show a significant decline. Their long-term potential to develop cardiomyopathy, left ventricular dysfunction and coronary artery disease is, therefore, considerably reduced.[20-23] The manifestations due to sleep apnea, hyperhidrosis, hypertrophic arthropathy and the potential risk of cancer, especially colonic, may also show reduction.[6,22]

Lack of remission of GH levels or its recurrent elevation after surgery is dependent on several factors. These include existence of high suprasellar lesions, tumors with a firm or fibrous consistency, often causing suprasellar arachnoidal breach or coexisting with multiple insinuations between major neurovascular bundles and perforators, and/or those infiltrating into the cavernous sinus, retrosellar region or the fronto-temporal region.[5-8,10,24] In our study group, 80 out of 115 (69.6%) patients had tumors that were confined to the

Table 5: Comparison of mean preoperative and follow-up basal and stimulated GH levels (stimulated GH estimated after oral glucose tolerance test) (*n*=101)

Tumor grade (Hardy)	Preoperative mean GH (μg/L)	Preoperative mean GH after OGTT (μg/L)	FU mean GH (μg/L)	FU mean GH after OGTT (μg/L)
Grade-o	23.1	21.9	6.0	5.3
Grade-A	24.1	23.9	4.0	3.9
Grade-A+E	13.0	12.1	5.9	7.5
Grade-B	33.4	36.5	7.7	5.8
Grade-B+E	33.3	32.1	5.4	6.0
Grade-C	20.1	19.5	1.5	1.9
Grade-C+E	28.9	28.3	18.5	15.9
Grade-D	28.7	25.8	26	25
Grade-D+E	21.8	22.3	16.4	16.2
Grade-E	23.04	20.5	12.7	10.5

OGTT – Oral glucose tolerance test; GH – Growth hormone; FU – Follow-up

Table 6: Cases in whom symptoms improved at FU after surgery despite of persistently high GH level

Tumor grade (Hardy)	Preoperative GH (μg/L)	Preoperative GH after OGTT (μg/L)	FU GH (μg/L)	FU GH after OGTT (μg/L)
Grade-A	25	25	24	23
Grade-B	32	35	33	33
Grade-B	33	33	10	4.8
Grade-C	26	28	33	26
Grade-D	32	32	25	25
Grade-D	30	30	24	25

OGTT – Oral glucose tolerance test; GH – Growth hormone; FU – Follow-up

sella with up to 3 cm suprasellar (and no parasellar) extension. The development of clinical manifestations of acromegaly in these functional adenomas led to their early detection before they attained a very large size. These lesions were, thus, easily accessible using the trans-sphenoidal approach. Thirty four (29.6%) patients also had a parasellar tumor extension. In consonance with literature, it was apparent from our study that lack of normalization of biochemical GH levels following surgical intervention was often associated with tumors with a large supra- (greater than 3 cm; modified Hardy's grade D) or parasellar (Hardy's grade E) extension.

In a functional pituitary adenoma, the aim of surgery is complete surgical extirpation of the functional tissue in order to normalize hormonal levels. Thus, aggressive tumor removal is advocated whenever possible. For large extensions, often multiple approaches may be required. These include a staged TSS to access the suprasellar component of the tumor that descends from the suprasellar to the sellar region after the first stage; or, a TSS followed by or combined with a transcranial approach (frontotemporal trans-sylvian, unilateral subfrontal or bifrontal interhemispheric approach).[5,10,13,18,20-27] In our series, a two-staged removal was effective in normalizing GH levels in 10 patients in whom the GH levels after the first surgery were continuing at persistently high levels.

Eighteen of our patients had a microadenoma located within the pituitary gland. For its precise preoperative localization within the pituitary gland substance, eight of these patients required a thin-section coronal dynamic contrast MR imaging.[28] Delay in contrast enhancement of the lesion compared with rest of the pituitary gland on serial coronal contrast MR imaging, shift of the pituitary stalk and asymmetry in the superior margins of the pituitary gland on comparison of both sides helped in radiological localization of the microadenoma. During surgery, these functioning yellowish-grey microadenomas could clearly be distinguished from the reddish-brown normal pituitary gland both by their colour and softer consistency.

Six patients had inadequate control of the disease according to the criteria of cure suggested in the consensus statement by Giustina *et al*. Thus, the disease was rendered clinically inactive following surgery although they do not satisfy the strict criteria for cure.[11] In such patients, the acromegaly is considered controlled but not cured.[6,11] All these six patients were adults in whom there was clinical improvement of acromegalic features following surgery although their biochemical levels did not normalize. They are being kept under close observation with regular biochemical testing (including IGF-1 levels) as maintenance of remission of clinical signs and symptoms of acromegaly may often achieve normal life expectancy.[23] If these patient remain clinically asymptomatic (except for persisting acral skeletal enlargement), a close FU without therapy will suffice. If even minor clinical aggravations such as glucose intolerance emerge or if the IGF-1 level becomes high, further therapeutic intervention may be necessary.

Long-term studies have shown that a reduction of the mean GH day curve or random GH levels to less than 2.5 μg/L is required to normalize the elevated mortality rate in acromegalic patients.[11,12,13] Sheaves *et al.* reported biochemical remission (mean GH less than 2.5 μg/L) in 61% of patients with microadenomas and in 23% with macroadenomas.[13] Osman *et al.* in his 79 patients with acromegaly found post-glucose GH levels after TSS to be less than 1 μg/L in 49% of patients and less than 2.5 μg/L in 76% of patients during the immediate postoperative testing.[22] Ahmed *et al.*, evaluating 139 patients who underwent an initial TSS reported an overall remission in 67% patients (91% in patients with microadenomas and 46% in those with macroadenomas) with the remission criteria being a mean GH of less than 2.5 μg/L.[29] Several other series achieved similar high remission rates for microadenomas approximating nearly 60%. However, for macroadenomas, the remission rates were much lower (approximately 14-35%).[2,6,13,21,23,26,27] In our series, the initial remission rate using the same biochemical criteria was achieved in nearly 82.2% (83 out of 101) patients. However, with subsequent 7 recurrences, the subsequent remission rate fell to 75.3%. The reported recurrence rate in patients with acromegaly ranges from 2 to 14%.[13,25] This recurrence rate is low enough to avoid recommending prophylactic radiation in every case following successful surgical extirpation of the pituitary adenoma. However, due to the persistent risk of recurrence, a regular FU examination every 6 to 12 months is mandatory in every case.[6]

A correlation exists between 24-hour mean GH and IGF-1 levels in acromegaly. Acromegaly in the absence of high IGF-1 levels is extremely rare; therefore, this relationship makes IGF-1 an ideal screening test.[6] Perhaps the addition of serial preoperative and FU assessment of IGF-1 in every patient in our series would have increased the sensitivity of detection of remission and subsequent relapses in our series. However, we relied on the basal serum GH levels and the nadir achieved on OGTT to assess for active acromegaly at FU, as IGF-1 was not being routinely performed during the duration of the study. Moreover, there is debate in the literature on whether GH or IGF-1 levels are more reliable to evaluate treatment of acromegaly.[16] It has been reported that 15% of acromegalic patients with GH levels less than 1 μg/L after treatment demonstrate abnormal IGF-1 levels, while 15% of patients with normal IGF-1 fail to suppress GH levels to less than 1 μg/L during the OGTT. Tzanela states that GH and IGF-1 levels represent two different aspects of disease activity in acromegaly. While IGF-1 evaluates the secretory function of the somatotropes, GH level provides evidence of the presence or absence of functional autonomy of these cells.[16] Stoffel-Wagner *et al.* further affirm that only by means of the OGTT could patients with active acromegaly be completely distinguished from the control subjects and from cured patients. IGF-1 and free IGF-1 are useful in the diagnosis of acromegaly, but of limited value in the FU of acromegalic patients after treatment.[15]

We administered radiation therapy in patients who were clinically symptomatic and had persistently high GH levels following surgery. In all cases where RT is being administered, it is recommended that tumor debulking during the initial surgery should ensure that the tumor capsule is at least 5 mm away from the optic chiasma because of the potential for damage to vision during pituitary irradiation.[6,30-32] Radiotherapy also impairs gonadotropin function. This is of special importance in young adults who desire fertility. Some of our patients presented with hypopituitarism following successful surgical intervention. This makes it mandatory to assess thyroid and gonadal axis after 6 to 12 weeks in every case and if required give supplemental hormonal therapy. Those patients, who have also received radiation therapy, however, often require lifelong monitoring of pituitary functions as hypopituitarism may manifest even after 15 years of treatment.[30]

Conclusions

The remission rate following surgical intervention in acromegalic patients with pituitary adenoma was approximately 75.3% in the available follow-up (FU). It was possible to perform an effective surgical extirpation of tumors having 3 cm or less suprasellar height and without parasellar extension with no clinical recurrence at FU after the initial remission. The parasellar extension of the tumor was the most common cause of recurrence. A continuous monitoring is mandatory to pick up relapsed cases as well as those who develop delayed signs of hypopituitarism. A subset of patients who show clinical remission but may still not confirm to the biochemical criteria of "cure" using OGTT-suppressed GH levels may be followed up without additional therapy unless clinical signs reappear or the serum GH or IGF-1 levels progressively increase.

Acknowledgment

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